

## **Amendments to the Claims:**

This listing of claims will replace all prior versions, and listings, of claims in the application:

### **Listing of claims:**

For the convenience of the Examiner, all claims being examined are presented below.

1. **(Cancelled)** A composition including a polypeptide comprising an antibody-based antigen-binding domain of human composition with binding specificity for an antigen expressed on the surface of a human cell, wherein treating cells expressing said antigen with a multivalent polypeptide having two or more of said antigen-binding domains causes or leads to killing of said cells in a manner where neither cytotoxic entities nor immunological mechanisms are needed for said killing.
2. **(Cancelled)** A composition including a polypeptide comprising an antibody-based antigen-binding domain which binds to human HLA-DR with a  $K_d$  of 1  $\mu$ M or less, wherein treating cells expressing HLA-DR with a multivalent polypeptide having two or more of said antigen-binding domains causes or leads to killing of said cells in a manner where neither cytotoxic entities nor immunological mechanisms are needed for said killing.
3. **(Cancelled)** A composition including a multivalent polypeptide comprising a plurality of antibody-based antigen-binding domains of human composition which specifically bind to human HLA-DR, wherein treating cells expressing HLA-DR with said multivalent polypeptide causes or leads to killing of said cells in a manner where neither cytotoxic entities nor immunological mechanisms are needed for said killing, wherein said antigen-binding domains individually bind to human HLA-DR with a  $K_d$  of 1  $\mu$ M or less.
4. **(Cancelled)** A composition including a multivalent polypeptide comprising a plurality of antibody-based antigen-binding domains of human composition which specifically bind to human HLA-DR, wherein treating cells expressing HLA-DR with said multivalent polypeptide causes or leads to killing of said cells in a manner where neither cytotoxic

- entities nor immunological mechanisms are needed for said cell killing, wherein said multivalent polypeptide has an  $EC_{50}$  of 100 nM or less for killing activated lymphoid cells.
5. **(Cancelled)** A composition including a polypeptide comprising at least one antibody-based antigen-binding domain that binds to human HLA-DR with a  $K_d$  of 1  $\mu$ M or less, said antigen-binding domain being isolated by a method which includes isolation of VL and VH domains of human composition from a recombinant antibody library by ability to bind to at least one epitope of human HLA-DR, wherein treating cells expressing HLA-DR with a multivalent polypeptide having two or more of said antigen binding domains causes or leads to killing of said cells in a manner where neither cytotoxic entities nor immunological mechanisms are needed for said killing.
  6. **(Cancelled)** The composition of claim 5, wherein the method for isolating the antigen-binding domain includes the further steps of:
    - a. generating a library of variants of at least one of the CDR1, CDR2 and CDR3 sequences of one or both of the VL and VH domains, and
    - b. isolation of VL and VH domains from the library of variants by ability to bind to human HLA-DR with a  $K_d$  of 1  $\mu$ M or less.
  7. **(Currently Amended)** The composition of any one of claims ~~1-622-29~~, wherein the multivalent polypeptide has an  $EC_{50}$  for killing transformed cells at least 5-fold lower than the  $EC_{50}$  for killing normal cells.
  8. **(Currently Amended)** The composition of any one of claims ~~1-622-29~~, wherein the multivalent polypeptide has an  $EC_{50}$  for killing activated cells at least 5-fold lower than the  $EC_{50}$  for killing unactivated cells.
  9. **(Currently Amended)** The composition of any of claims ~~1-622-29~~, wherein the multivalent polypeptide has an  $EC_{50}$  of 50 nM or less for killing transformed cells.

10. **(Currently Amended)** The composition of any of claims ~~1-622-29~~, wherein the multivalent polypeptide has an EC<sub>50</sub> for killing lymphoid tumor cells of 10 nM or less.
11. **(Currently Amended)** The composition of any of claims ~~1-622-29~~, wherein the multivalent polypeptide kills activated lymphoid cells.
12. **(Original)** The composition of claim 11, wherein said activated lymphoid cells are lymphoid tumor cells representing a disease selected from the group consisting of B cell non-Hodgkin lymphoma, B cell lymphoma, B cell acute lymphoid leukemia, Burkitt lymphoma, Hodgkin lymphoma, hairy cell leukemia, acute myeloid leukemia, T cell lymphoma, T cell non-Hodgkin lymphoma, chronic myeloid leukemia, chronic lymphoid leukemia, and multiple myeloma.
13. **(Currently Amended)** The composition of claim 11, wherein said activated lymphoid cells are from a cell line selected from the group consisting of PRIESS (ECACC Accession No: 86052111), GRANTA-519 (DSMZ Accession No: ACC 342), and KARPAS-422 (DSMZ Accession No: ACC 32), ~~KARPAS-299, DOHH 2, SR-786, MHH-CALL 4, MN-60, BJAB, RAJI, L-428, HDLM 2, HD-MY-Z, KM-H2, L1236, BONNA-12, HC-1, NALM-1, L-363, EOL-1, LP-1, RPMI-8226, and MHH-PREB-1 cell lines.~~
14. **(Currently Amended)** The composition of any of claims ~~1-622-29~~, wherein the multivalent polypeptide has an EC<sub>50</sub> of 100 nM or less for killing cells from ~~of at least one of lymphoid tumor cell lines selected from the group consisting of KARPAS-422 (DSMZ Accession No: ACC 32) DOHH 2, SR-786, MHH-CALL 4, MN-60, HD-MY-Z, NALM-1 and LP-1.~~
15. **(Currently Amended)** The composition of any of claims ~~1-622-29~~, wherein the multivalent polypeptide has an EC<sub>50</sub> of 50 nM or less for killing cells from at least one lymphoid tumor cell line selected from the group consisting of KARPAS-422 (ACC 32 from DSMZ), DOHH 2, MN-60, NALM-1 and LP-1.
16. **(Currently Amended)** The composition of any of claims ~~1-622-29~~, wherein the multivalent polypeptide has an EC<sub>50</sub> of 10 nM or less for killing cells from at least one B

cell lymphoblastoid cell line selected from the group consisting of LG2 and PRIESS (ECACC Accession No: 86052111).

17. **(Currently Amended)** The composition of any of claims ~~1-6~~22-29, wherein said cells are non-lymphoid cells that express MHC class II molecules.
18. **(Currently Amended)** The composition of ~~any of claims 1-6~~ 119, wherein said antigen-binding domain binds to the  $\beta$ -chain of HLA-DR.
19. **(Original)** The composition of claim 18, wherein said antigen-binding domain binds to the first domain of the  $\beta$ -chain of HLA-DR.
20. **(Currently Amended)** The composition of ~~any of claims 1-6~~ 119, wherein said antigen-binding domain binds to one or more HLA-DR types selected from the group consisting of DR1-0101, DR2-15021, DR3-0301, DR4Dw4-0401, DR4Dw10-0402, DR4Dw14-0404, DR6-1302, DR6-1401, DR8-8031, DR9-9012, DRw53-B4\*0101 and DRw52-B3\*0101.
21. **(Original)** The composition of claim 20, wherein said antigen-binding domain binds to at least 5 different of said HLA-DR types.
22. **(Currently Amended)** A composition including a polypeptide comprising an antibody-based antigen-binding domain of human composition with binding specificity for an antigen expressed on the surface of a human cell, wherein treating cells expressing said antigen with a multivalent polypeptide having two or more of said antigen-binding domains causes or leads to killing of said cells in a manner where neither cytotoxic entities nor immunological mechanisms are needed for said killing. ~~The composition of any one of claims 1-6;~~ wherein said antigen-binding domain includes a combination of a VH domain and a VL domain, wherein said combination is found in one of the clones selected from the group consisting of MS-GPC-1 (SEQ ID NOS 37 and 38, respectively), MS-GPC-6 (SEQ ID NOS 39 and 40, respectively), MS-GPC-8 (SEQ ID NOS 41 and 42, respectively), MS-GPC-10 (SEQ ID NOS 43 and 44, respectively), MS-GPC-8-1 (SEQ ID NOS 41 and 28, respectively), MS-GPC-8-6 (SEQ ID NOS 41 and 46, respectively), MS-GPC-8-9 (SEQ ID NOS 41 and 31, respectively), MS-GPC-8-10 (SEQ ID NOS 41

- and 48, respectively), MS-GPC-8-17 (SEQ ID NOS 41 and 50, respectively), MS-GPC-8-18 (SEQ ID NOS 41 and 31, respectively), MS-GPC-8-27 (SEQ ID NOS 41 and 52, respectively), MS-GPC-8-6-2 (SEQ ID NOS 41 and 45, respectively), MS-GPC-8-6-19 (SEQ ID NOS 41 and 47, respectively), MS-GPC-8-6-27 (SEQ ID NOS 41 and 49, respectively), MS-GPC-8-6-45 (SEQ ID NOS 41 and 51, respectively), MS-GPC-8-6-13 (SEQ ID NOS 41 and 54, respectively), MS-GPC-8-6-47 (SEQ ID NOS 41 and 53, respectively), MS-GPC-8-10-57 (SEQ ID NOS 41 and 56, respectively), MS-GPC-8-27-7 (SEQ ID NOS 41 and 55, respectively), MS-GPC-8-27-10 (SEQ ID NOS 41 and 57, respectively) and MS-GPC-8-27-41 (SEQ ID NOS 41 and 58, respectively).
23. **(Currently Amended)** A composition including a polypeptide comprising an antibody-based antigen-binding domain of human composition with binding specificity for an antigen expressed on the surface of a human cell, wherein treating cells expressing said antigen with a multivalent polypeptide having two or more of said antigen-binding domains causes or leads to killing of said cells in a manner where neither cytotoxic entities nor immunological mechanisms are needed for said killing, The composition of any one of claims 1-6, wherein said antigen-binding domain includes of a combination of HuCAL VH2 and HuCAL Vλ1, wherein the VH CDR3, VL CDR1 A and VL CDR3 is found in one of the clones selected from the group consisting of MS-GPC-1, (SEQ ID NOS 37 and 38, respectively), MS-GPC-8 (SEQ ID NOS 41 and 42, respectively), MS-GPC-10 (SEQ ID NOS 43 and 44, respectively), MS-GPC-8-1 (SEQ ID NOS 41 and 28, respectively), MS-GPC-8-6 (SEQ ID NOS 41 and 46, respectively), MS-GPC-8-9 (SEQ ID NOS 41 and 31, respectively), MS-GPC-8-10 (SEQ ID NOS 41 and 48, respectively), MS-GPC-8-17 (SEQ ID NOS 41 and 50, respectively), MS-GPC-8-18 (SEQ ID NOS 41 and 31, respectively), MS-GPC-8-27 (SEQ ID NOS 41 and 52, respectively), MS-GPC-8-6-2 (SEQ ID NOS 41 and 45, respectively), MS-GPC-8-6-19 (SEQ ID NOS 41 and 47, respectively), MS-GPC-8-6-27 (SEQ ID NOS 41 and 49, respectively), MS-GPC-8-6-45 (SEQ ID NOS 41 and 51, respectively), MS-GPC-8-6-13 (SEQ ID NOS 41 and 54, respectively), MS-GPC-8-6-47 (SEQ ID NOS 41 and 53, respectively), MS-GPC-8-10-57 (SEQ ID NOS 41 and 56, respectively), MS-GPC-8-27-7 (SEQ ID NOS 41 and 55, respectively), MS-GPC-8-27-10 (SEQ ID NOS 41 and 57, respectively) and MS-GPC-8-27-41 (SEQ ID NOS 41 and 58, respectively).



24. **(Currently Amended)** A composition including a polypeptide comprising an antibody-based antigen-binding domain of human composition with binding specificity for an antigen expressed on the surface of a human cell, wherein treating cells expressing said antigen with a multivalent polypeptide having two or more of said antigen-binding domains causes or leads to killing of said cells in a manner where neither cytotoxic entities nor immunological mechanisms are needed for said killing. ~~The composition of any one of claims 1-6,~~ wherein said antigen-binding domain includes a combination of HuCAL VH2 and HuCAL V $\lambda$ 1, wherein the VH CDR3 sequence is taken from the consensus CDR3 sequence

XXXXRGXFDX (SEQ ID No. 1)

wherein each X independently represents any amino acid residue; and/or

wherein the VL CDR3 sequence is taken from the consensus CDR3 sequence

QSYDXXXX (SEQ ID No. 2)

wherein each X independently represents any amino acid residue.

25. **(Currently Amended)** The composition of claim 24, wherein the VH CDR3 sequence of said antigen-binding domain is SPRYRGAFDY (SEQ ID No. 3) and/or the VL CDR3 sequence of said antigen-binding domain is QSYDLIRH (SEQ ID No. 4) or QSYDMNVH (SEQ ID No. 5).

26. **(Currently Amended)** A composition including a polypeptide comprising an antibody-based antigen-binding domain of human composition with binding specificity for an antigen expressed on the surface of a human cell, wherein treating cells expressing said antigen with a multivalent polypeptide having two or more of said antigen-binding domains causes or leads to killing of said cells in a manner where neither cytotoxic entities nor immunological mechanisms are needed for said killing. ~~The composition of any one of claims 1-6,~~ wherein said antigen-binding domain competes for antigen binding with an antibody including a combination of HuCAL VH2 and HuCAL V $\lambda$ 1, wherein the VH CDR3 sequence is taken from the consensus CDR3 sequence

XXXXRGXFDX (SEQ ID No. 1)

each X independently represents any amino acid residue; and/or  
the VL CDR3 sequence is taken from the consensus CDR3 sequence

QSYDXXXX (SEQ ID No. 2)

each X independently represents any amino acid residue.

27. **(Currently Amended)** The composition of claim 26, wherein the VH CDR3 sequence of said antibody is SPRYRGAFDY (SEQ ID No. 3) and/or the VL CDR3 sequence of said antibody is QSYDLIRH (SEQ ID No. 4) or QSYDMNVH (SEQ ID No. 5).

28. **(Currently Amended)** A composition including a polypeptide comprising an antibody-based antigen-binding domain of human composition with binding specificity for an antigen expressed on the surface of a human cell, wherein treating cells expressing said antigen with a multivalent polypeptide having two or more of said antigen-binding domains causes or leads to killing of said cells in a manner where neither cytotoxic entities nor immunological mechanisms are needed for said killing. ~~The composition of any one of claims 1-6,~~ wherein said antigen-binding domain includes a VL CDR1 sequence represented in the general formula

SGSXXNIGXNYVX (SEQ ID No. 6)

wherein each X independently represents any amino acid residue.

29. **(Original)** The composition of claim 28, wherein the CDR1 sequence is SGSESNIGNNYVQ (SEQ ID No. 7).
30. **(Cancelled)** The composition of any of claims 1-6, wherein the mechanism of said killing involves an innate pre-programmed process of said cell.
31. **(Cancelled)** The composition of claim 30, wherein said killing is non-apoptotic.
32. **(Cancelled)** The composition of claim 30, wherein said killing is dependent on the action of non-caspase proteases, and/or wherein said killing cannot be inhibited by zVAD-fmk or zDEVD-fmk.

33. **(Currently Amended)** The composition of any one of claims ~~1-6~~22-29, wherein said antibody-based antigen-binding domain is part of a multivalent polypeptide including at least a F(ab')<sub>2</sub> antibody fragment or a mini-antibody fragment.
34. **(Currently Amended)** The composition of any one of claims ~~1-6~~22-29, wherein said antibody-based antigen-binding domain is part of a multivalent polypeptide comprising at least two monovalent antibody fragments selected from Fv, scFv, dsFv and Fab fragments, and further comprises a cross-linking moiety or moieties.
35. **(Currently Amended)** The composition of any one of claims ~~1-6~~22-29, wherein said antibody-based antigen-binding domain is part of a multivalent polypeptide comprising at least one full antibody selected from the antibodies of classes IgG<sub>1</sub>, 2a, 2b, 3, 4, IgA, and IgM.
36. **(Currently Amended)** The composition of any one of claims ~~1-6~~22-29, wherein said antibody-based antigen-binding domain is part of a multivalent polypeptide that is formed prior to binding to a cell.
37. **(Currently Amended)** The composition of any one of claims ~~1-6~~22-29, wherein said antibody-based antigen-binding domain is part of a multivalent polypeptide that is formed after binding to a cell.
38. **(Currently Amended)** The composition of any one of claims ~~1-6~~22-29, wherein the antigen binding ~~sites~~domain ~~are~~is cross-linked to a polymer.
39. **(Withdrawn)** A nucleic acid comprising a protein coding sequence for an antigen-binding domain comprised in any of claims 1-6, or a multivalent polypeptide thereof.
40. **(Withdrawn)** A vector comprising the nucleic acid of claim 39, and a transcriptional regulatory sequence operably linked thereto.
41. **(Withdrawn)** A host cell harboring a nucleic acid of claim 39.
42. **(Withdrawn)** A method for the production of composition comprising a multivalent polypeptide that causes or leads to killing of cells in a manner where neither cytotoxic



- entities nor immunological mechanisms are needed for said killing, comprising culturing the cells of claim 41 under conditions wherein the nucleic acid is expressed either as a multivalent polypeptide or as a polypeptide comprising at least one antigen binding domains which is subsequently treated to form a multivalent polypeptide composition.
43. **(Currently Amended)** The composition of any one of claims ~~1-6~~22-29, formulated in a pharmaceutically acceptable carrier and/or diluent.
44. **(Withdrawn)** The use of a composition of any of claims 1-6, for preparing a pharmaceutical preparation for the treatment of animals.
45. **(Withdrawn)** The use of a nucleic acid of claim 39 for preparing a pharmaceutical preparation for the treatment of animals.
46. **(Withdrawn)** The use of a host cell of claim 41 for preparing a pharmaceutical preparation for the treatment of animals.
47. **(Withdrawn)** The use of the method of claim 42 for preparing a pharmaceutical preparation for the treatment of animals.
48. **(Withdrawn)** The use according to claim 44, wherein said animal is a human.
49. **(Withdrawn)** The use according to claim 44, for the treatment of cell proliferative disorders, wherein said antibody-based antigen binding domain is part of a multivalent polypeptide.
50. **(Withdrawn)** The use according to claim 49, wherein said treatment is the treatment of disorders involving transformed cells expressing MHC class II antigens.
51. **(Withdrawn)** The use according claim 49, wherein said treatment is the treatment of a disorder selected from B cell non-Hodgkin lymphoma, B cell lymphoma, B cell acute lymphoid leukemia, Burkitt lymphoma, Hodgkin lymphoma, hairy cell leukemia, acute myeloid leukemia, T cell lymphoma, T cell non-Hodgkin lymphoma, chronic myeloid leukemia, chronic lymphoid leukemia, or multiple myeloma.

52. **(Withdrawn)** The use according to claim 44, wherein said treatment is the treatment of disorders involving unwanted activation of cells of the immune system, such as lymphoid cells expressing MHC class II.
53. **(Withdrawn)** The use according to claim 44, wherein said treatment is the treatment of a disorder selected from rheumatoid arthritis, juvenile arthritis, multiple sclerosis, Grave's disease, insulin-dependent diabetes, narcolepsy, psoriasis, systemic lupus erythematosus, ankylosing spondylitis, transplant rejection, graft vs. host disease, Hashimoto's disease, myasthenia gravis, pemphigus vulgaris, glomerulonephritis, thyroiditis, pancreatitis, insulinitis, primary biliary cirrhosis, irritable bowel disease or Sjogren syndrome.
54. **(Withdrawn)** The use according to claim 44, wherein said disorder is selected from myasthenia gravis, rheumatoid arthritis, multiple sclerosis, transplant rejection or graft vs. host disease.
55. **(Currently Amended)** A diagnostic composition including the composition of any of claims ~~1-6~~ 22-29.
56. **(Original)** The diagnostic composition of claim 55, further comprising a cross-linking moiety or moieties.
57. **(Withdrawn)** A method for killing a cell expressing an antigen on the surface of said cell comprising the step of treating the cell with a plurality of antigen-binding domains of any one of claims 1-6, wherein said antibody-based antigen-binding domains are part of a multivalent polypeptide, and where neither cytotoxic entities nor immunological mechanisms are needed to causes or leads to said killing.
58. **(Withdrawn)** A method to identify patients that can be treated with a composition of any of claims 1-6, formulated in a pharmaceutically acceptable carrier and/or diluent comprising:
- a. isolating cells from a patient;
  - b. contacting said cells with the composition of any of claims 1-6; and,

- c. measuring the degree of killing or immunosuppression of said cells.
59. **(Currently Amended)** A kit to identify patients that can be treated with a composition of any of claims ~~1-6~~22-29, formulated in a pharmaceutically acceptable carrier and/or diluent comprising:
- a. a composition of any of claims ~~1-6~~22-29; and
  - b. means to measure the degree of killing or immunosuppression of said cells.
60. **(Currently Amended)** A kit comprising:
- a. a composition according to any one of claims ~~1-6~~22-29, and
  - b. a cross-linking moiety.
61. **(Currently Amended)** A kit comprising:
- a. a composition according to any one of claims ~~1-6~~22-29, and
  - b. a detectable moiety or moieties, and
  - c. reagents and/or solutions to effect and/or detect binding of (a) to an antigen.
62. **(Currently Amended)** ~~A cytotoxic composition comprising a~~ The composition of any one of claims ~~1-6~~22-29 operably linked to a cytotoxic agent.
63. **(Currently Amended)** ~~An immunogenic composition comprising a~~ The composition of any one of claims ~~1-6~~22-29 operably linked to an immunogenic agent.
64. **(Withdrawn)** A method to kill a cell comprising contacting said cell with a composition of any one of claims 1-6 operably linked a cytotoxic or immunogenic agent.
65. **(Withdrawn)** The use of a composition of any one of claims 1-6 operable linked a cytotoxic or immunogenic agent for preparing a pharmaceutical preparation for the treatment of animals.

66. **(Cancelled)** A composition including a polypeptide comprising at least one antibody-based antigen-binding domain with a binding specificity for a human MHC class II antigen with a  $K_d$  of 1  $\mu$ M or less, wherein treating cells expressing said antigen with said polypeptide causes or leads to suppression of an immune response.
67. **(Currently Amended)** A composition including a polypeptide comprising at least one antibody-based antigen-binding domain with a binding specificity for human HLA-DR antigen, wherein treating cells expressing HLA-DR with said polypeptide causes or leads to suppression of an immune response, and wherein said antigen-binding domain includes a combination of a VH domain and a VL domain, wherein said combination is found in one of the clones taken from the group consisting of MS-GPC-1, (SEQ ID NOS 37 and 38, respectively), MS-GPC-6 (SEQ ID NOS 39 and 40, respectively), MS-GPC-8 (SEQ ID NOS 41 and 42, respectively), MS-GPC-10 (SEQ ID NOS 43 and 44, respectively), MS-GPC-8-1 (SEQ ID NOS 41 and 28, respectively), MS-GPC-8-6 (SEQ ID NOS 41 and 46, respectively), MS-GPC-8-9 (SEQ ID NOS 41 and 31, respectively), MS-GPC-8-10 (SEQ ID NOS 41 and 48, respectively), MS-GPC-8-17 (SEQ ID NOS 41 and 50, respectively), MS-GPC-8-18 (SEQ ID NOS 41 and 31, respectively), MS-GPC-8-27 (SEQ ID NOS 41 and 52, respectively), MS-GPC-8-6-2 (SEQ ID NOS 41 and 45, respectively), MS-GPC-8-6-19 (SEQ ID NOS 41 and 47, respectively), MS-GPC-8-6-27 (SEQ ID NOS 41 and 49, respectively), MS-GPC-8-6-45 (SEQ ID NOS 41 and 51, respectively), MS-GPC-8-6-13 (SEQ ID NOS 41 and 54, respectively), MS-GPC-8-6-47 (SEQ ID NOS 41 and 53, respectively), MS-GPC-8-10-57 (SEQ ID NOS 41 and 56, respectively), MS-GPC-8-27-7 (SEQ ID NOS 41 and 55, respectively), MS-GPC-8-27-10 (SEQ ID NOS 41 and 57, respectively) and MS-GPC-8-27-41 (SEQ ID NOS 41 and 58, respectively).
68. **(Cancelled)** A composition including a polypeptide comprising at least one antibody-based antigen-binding domain with a binding specificity for a human MHC class II antigen with a  $K_d$  of 1  $\mu$ M or less, said antigen-binding domain being isolated by a method which includes isolation of VL and VH domains of human composition from a recombinant antibody library by ability to bind to human MHC class II antigen, wherein

treating cells expressing MHC Class II with said polypeptide causes or leads to suppression of an immune response.

69. **(Cancelled)** The composition of claim 68, wherein the method for isolating the antigen-binding domain includes the further steps of:
- a. generating a library of variants at least one of the CDR1, CDR2 and CDR3 sequences of one or both of the VL and VH domains, and
  - b. isolation of VL and VH domains from the library of variants by ability to bind to human MHC class II antigen with a  $K_d$  of 1  $\mu$ M or less;
  - c. (optionally) repeating steps (a) and (b) with at least one other of the CDR1, CDR2 and CDR3 sequences.
70. **(Currently Amended)** The composition of any of claims ~~67, 68 or 69~~ 80-87, wherein said antigen-binding domain binds to HLA-DR.
71. **(Currently Amended)** The composition of ~~any of claims 66-69~~ claim 67 or 70, wherein said antigen-binding domain binds to the  $\beta$ -chain of HLA-DR.
72. **(Original)** The composition of claim 71, wherein said antigen-binding domain binds to an epitope of the first domain of the  $\beta$ -chain of HLA-DR.
73. **(Currently Amended)** The composition of any of claims ~~66-69~~ 67, 80-87, wherein said cells are lymphoids cells.
74. **(Currently Amended)** The composition of any of claims ~~66-69~~ 67, 80-87, wherein said cells are non-lymphoid cells and express MHC class II antigens.
75. **(Currently Amended)** The composition of any of claims ~~66-69~~ 67, 80-87, having an  $IC_{50}$  for suppressing an immune response of 1  $\mu$  M or less.
76. **(Currently Amended)** The composition of any of claims ~~66-69~~ 67, 80-87, having an  $IC_{50}$  for inhibition of IL-2 secretion of 1  $\mu$  M or less.



77. **(Currently Amended)** The composition of any of claims ~~66-69~~ 67, 80-87, having an  $IC_{50}$  for inhibiting T cell proliferation of  $1 \mu M$  or less.
78. **(Currently Amended)** The composition of any of claims ~~66-69~~ 67, 80-87, wherein said antigen-binding domain binds to one or more HLA-DR types selected from the group consisting of DR1-0101, DR2-15021, DR3-0301, DR4Dw4-0401, DR4Dw10-0402, DR4Dw14-0404, DR6-1302, DR6-1401, DR8-8031, DR9-9012, DRw53-B4\*0101 and DRw52-B3\*0101.
79. **(Original)** The composition of claim 78, wherein said antigen-binding domain binds to at least 5 different of said HLA-DR types.
80. **(Currently Amended)** A composition including a polypeptide comprising at least one antibody-based antigen-binding domain with a binding specificity for a human MHC class II antigen with a  $K_d$  of  $1 \mu M$  or less, wherein treating cells expressing said antigen with said polypeptide causes or leads to suppression of an immune response ~~The composition of any of claims 66-69~~, wherein said antigen-binding domain includes a combination of a VH domain and a VL domain, wherein said combination is found in one of the clones taken from the group consisting of MS-GPC-1 (SEQ ID NOS 37 and 38, respectively), MS-GPC-6 (SEQ ID NOS 39 and 40, respectively), MS-GPC-8 (SEQ ID NOS 41 and 42, respectively), MS-GPC-10 (SEQ ID NOS 43 and 44, respectively), MS-GPC-8-1 (SEQ ID NOS 41 and 28, respectively), MS-GPC-8-6 (SEQ ID NOS 41 and 46, respectively), MS-GPC-8-9 (SEQ ID NOS 41 and 31, respectively), MS-GPC-8-10 (SEQ ID NOS 41 and 48, respectively), MS-GPC-8-17 (SEQ ID NOS 41 and 50, respectively), MS-GPC-8-18 (SEQ ID NOS 41 and 31, respectively), MS-GPC-8-27 (SEQ ID NOS 41 and 52, respectively), MS-GPC-8-6-2 (SEQ ID NOS 41 and 45, respectively), MS-GPC-8-6-19 (SEQ ID NOS 41 and 47, respectively), MS-GPC-8-6-27 (SEQ ID NOS 41 and 49, respectively), MS-GPC-8-6-45 (SEQ ID NOS 41 and 51, respectively), MS-GPC-8-6-13 (SEQ ID NOS 41 and 54, respectively), MS-GPC-8-6-47 (SEQ ID NOS 41 and 53, respectively), MS-GPC-8-10-57 (SEQ ID NOS 41 and 56, respectively), MS-GPC-8-27-7 (SEQ ID NOS 41 and 55, respectively), MS-GPC-8-27-10 (SEQ ID NOS 41 and 57, respectively) and MS-GPC-8-27-41 (SEQ ID NOS 41 and 58, respectively).

81. **(Currently Amended)** A composition including a polypeptide comprising at least one antibody-based antigen-binding domain with a binding specificity for a human MHC class II antigen with a  $K_d$  of 1  $\mu$ M or less, wherein treating cells expressing said antigen with said polypeptide causes or leads to suppression of an immune response ~~The composition of any of claims 66-69,~~ wherein said antigen-binding domain includes of a combination of HuCAL VH2 and HuCAL V $\lambda$ 1, wherein the VH CDR3, VL CDR1 A and VL CDR3 is found in one of the clones selected from the group consisting of MS-GPC-1 (SEQ ID NOS 37 and 38, respectively), MS-GPC-8 (SEQ ID NOS 41 and 42, respectively), MS-GPC-10 (SEQ ID NOS 43 and 44, respectively), MS-GPC-8-1 (SEQ ID NOS 41 and 28, respectively), MS-GPC-8-6 (SEQ ID NOS 41 and 46, respectively), MS-GPC-8-9 (SEQ ID NOS 41 and 31, respectively), MS-GPC-8-10 (SEQ ID NOS 41 and 48, respectively), MS-GPC-8-17 (SEQ ID NOS 41 and 50, respectively), MS-GPC-8-18 (SEQ ID NOS 41 and 31, respectively), MS-GPC-8-27 (SEQ ID NOS 41 and 52, respectively), MS-GPC-8-6-2 (SEQ ID NOS 41 and 45, respectively), MS-GPC-8-6-19 (SEQ ID NOS 41 and 47, respectively), MS-GPC-8-6-27 (SEQ ID NOS 41 and 49, respectively), MS-GPC-8-6-45 (SEQ ID NOS 41 and 51, respectively), MS-GPC-8-6-13 (SEQ ID NOS 41 and 54, respectively), MS-GPC-8-6-47 (SEQ ID NOS 41 and 53, respectively), MS-GPC-8-10-57 (SEQ ID NOS 41 and 56, respectively), MS-GPC-8-27-7 (SEQ ID NOS 41 and 55, respectively), MS-GPC-8-27-10 (SEQ ID NOS 41 and 57, respectively) and MS-GPC-8-27-41 (SEQ ID NOS 41 and 58, respectively).
82. **(Currently Amended)** A composition including a polypeptide comprising at least one antibody-based antigen-binding domain with a binding specificity for a human MHC class II antigen with a  $K_d$  of 1  $\mu$ M or less, wherein treating cells expressing said antigen with said polypeptide causes or leads to suppression of an immune response ~~The composition of any of claims 66-69,~~ wherein said antigen-binding domain includes a combination of HuCAL VH2 and HuCAL V $\lambda$ 1, wherein the VH CDR3 sequence is taken from the consensus CDR3 sequence
- XXXXRGXFDX (SEQ ID No. 1)
- wherein each X independently represents any amino acid residue; and/or
- wherein the VL CDR3 sequence is taken from the consensus CDR3 sequence

QSYDXXXX (SEQ ID No. 2)

wherein each X independently represents any amino acid residue.

83. **(Currently Amended)** The composition of claim 82, wherein the VH CDR3 sequence of said antigen-binding domain is SPRYRGAFDY (SEQ ID No. 3) and/or the VL CDR3 sequence of said antigen-binding domain is QSYDLIRH (SEQ ID No. 4) or QSYDMNVH (SEQ ID No. 5).

84. **(Currently Amended)** A composition including a polypeptide comprising at least one antibody-based antigen-binding domain with a binding specificity for a human MHC class II antigen with a  $K_d$  of 1  $\mu$ M or less, wherein treating cells expressing said antigen with said polypeptide causes or leads to suppression of an immune response ~~The composition of any of claims 66-69, wherein said antigen-binding domain competes for antigen binding with an antibody including a combination of HuCAL VH2 and HuCAL V $\lambda$ 1, wherein the VH CDR3 sequence is taken from the consensus CDR3 sequence~~ XXXXRGXFDX (SEQ ID No. 1)

each X independently represents any amino acid residue; and/or

the VL CDR3 sequence is taken from the consensus CDR3 sequence

QSYDXXXX (SEQ ID No. 2)

each X independently represents any amino acid residue.

85. **(Currently Amended)** The composition of claim 84, wherein the VH CDR3 sequence of said antibody is SPRYRGAFDY (SEQ ID No. 3) and/or the VL CDR3 sequence of said antibody is QSYDLIRH (SEQ ID No. 4) or QSYDMNVH (SEQ ID No. 5).

86. **(Currently Amended)** A composition including a polypeptide comprising at least one antibody-based antigen-binding domain with a binding specificity for a human MHC class II antigen with a  $K_d$  of 1  $\mu$ M or less, wherein treating cells expressing said antigen with said polypeptide causes or leads to suppression of an immune response ~~The composition of any of claims 66-69, wherein said antigen-binding domain includes a VL CDR1 sequence represented in the general formula~~

SGSXXNIGXNYVX (SEQ ID No. 6)

wherein each X independently represents any amino acid residue.

87. **(Original)** The composition of claim 86, wherein the CDR1 sequence is SGSESNIGNNYVQ (SEQ ID No. 7).
88. **(Cancelled)** The composition of any one of claims 66-69, wherein said suppression of an immune response is brought about by or manifests itself in down-regulation of expression of said antigen expressed on the surface of said cell.
89. **(Cancelled)** The composition of any one of claims 66-69, wherein said suppression of an immune response is brought about by or manifests itself in inhibition of the interaction between said cell and other cells, wherein said interaction would normally lead to an immune response.
90. **(Cancelled)** The composition of any one of claims 66-69, wherein said suppression of the immune response is brought about by or manifests itself in the killing of said cells.
91. **(Cancelled)** The composition of claim 90, wherein said killing is mediated by binding of a plurality of antigen-binding domains, wherein said antibody-based antigen-binding domains are part of a multivalent polypeptide, and where neither cytotoxic entities nor immunological mechanisms are needed to causes or leads to said killing.
92. **(Currently Amended)** The composition of any of claims ~~66-69~~ 67, 80-87, formulated in a pharmaceutically acceptable carrier and/or diluent.
93. **(Original)** A pharmaceutical preparation comprising the composition of claim 75 in an amount sufficient to suppress an immune response in an animal.
94. **(Original)** A pharmaceutical preparation comprising the composition of claim 76 in an amount sufficient to inhibit IL-2 secretion in an animal.
95. **(Original)** A pharmaceutical preparation comprising the composition of claim 77 in an amount sufficient to inhibit T cell proliferation in an animal.

96. **(Withdrawn)** The use of a composition of any one of claims 66-69, for preparing a pharmaceutical preparation for the treatment of animals, such as where said animals are human.
97. **(Withdrawn)** A nucleic acid including a protein coding sequence for a polypeptide of the composition of any of claims 66-69.
98. **(Withdrawn)** A vector comprising the coding sequence of claim 97, and a transcriptional regulatory sequence operably linked thereto.
99. **(Withdrawn)** A host cell harboring a nucleic acid selected from the group consisting of: a nucleic acid of claim 97 or the vector of claim 98.
100. **(Withdrawn)** A method for the production of an immunosuppressive composition, comprising culturing the cells of claim 99 under conditions wherein the nucleic acid is expressed.
101. **(Withdrawn)** A method for suppressing activation of a cell of the immune system, comprising treating the cell with a composition of any of claims 66-69.
102. **(Withdrawn)** A method for suppressing proliferation of a cell of the immune system, comprising treating the cell with a composition of any of claims 66-69.
103. **(Withdrawn)** A method for suppressing IL-2 secretion by a cell of the immune system, comprising treating the cell with a composition of any of claims 66-69.
104. **(Withdrawn)** A method for immunosuppressing a patient, comprising administering to the patient an effective amount of a composition of any of claims 66-69 to reduce the level of immunological responsiveness in the patient.
105. **(Withdrawn)** A method for killing a cell expressing an antigen on the surface of said cell comprising the step of treating the cell with a plurality of antigen-binding domains of any one of claims 66-69, wherein said antibody-based antigen-binding domains are part of a multivalent polypeptide, and where neither cytotoxic entities nor immunological



mechanisms are needed to causes or leads to said killing, such where said antigen is HLA-DR.

106. **(Withdrawn)** The use according to claim 96, wherein said treatment is the treatment of a disorder selected from rheumatoid arthritis, juvenile arthritis, multiple sclerosis, Grave's disease, insulin-dependent diabetes, narcolepsy, psoriasis, systemic lupus erythematosus, ankylosing spondylitis, transplant rejection, graft vs. host disease, Hashimoto's disease, myasthenia gravis, pemphigus vulgaris, glomerulonephritis, thyroiditis, pancreatitis, insulinitis, primary biliary cirrhosis, irritable bowel disease or Sjogren syndrome.
107. **(Withdrawn)** The use according to claim 96, wherein said treatment is the treatment of a disorder selected from myasthenia gravis, rheumatoid arthritis, multiple sclerosis, transplant rejection or graft vs. host disease.
108. **(Withdrawn)** A method of suppressing the interaction of a cell of the immune system with an other cell, comprising contacting the cell with the composition of any of claims 66-69.
109. **(Withdrawn)** A method for conducting a pharmaceutical business comprising:
  - a. isolating one or more antigen-binding domains that bind to antigens expressed on the surface of human cells;
  - b. generating a multivalent composition, such as multivalent polypeptide, comprising a plurality of said antigen-binding domains, which multivalent composition kills with an  $EC_{50}$  of 50nM or less transformed or activated cells that express said antigen, where neither cytotoxic entities nor immunological mechanisms are needed to cause or lead to said killing;
  - c. conducting therapeutic profiling of the multivalent composition, for efficacy and toxicity in animals;
  - d. preparing a package insert describing the multivalent composition for treatment of proliferative disorders; and,

- e. marketing the multivalent composition for treatment of proliferative disorders.
110. **(Withdrawn)** A method for conducting a life science business comprising:
- a. isolating one or more antigen-binding domains that bind to antigens expressed on the surface of human cells;
  - b. generating a multivalent composition, such as multivalent polypeptide, comprising a plurality of said antigen-binding domains, which multivalent composition kills with an  $EC_{50}$  of 50 nM or less transformed or activated cells expressing said antigen where neither cytotoxic entities nor immunological mechanisms are needed to cause or lead to said killing;
  - c. licensing, jointly developing or selling, to a third party, the rights for selling the multivalent composition.
111. **(Withdrawn)** The method of any of claims 109 or 110, wherein the antigen-binding domain is isolated by a method which includes:
- a. isolation of VL and VH domains of human composition from a recombinant antibody library by ability to bind to HLA-DR,
  - b. generating a library of variants at least one of the CDR1, CDR2 and CDR3 sequences of one or both of the VL and VH domains, and ,
  - c. isolation of VL and VH domains from the library of variants by ability bind to HLA-DR with a  $K_d$  of 1  $\mu$ M or less.
112. **(Withdrawn)** A method for conducting a pharmaceutical business comprising:
- a. isolating one or more antigen-binding domains that bind to MHC class II expressed on the surface of human cells with a  $K_d$  of 1  $\mu$ M or less;
  - b. generating a composition comprising said antigen-binding domains, which composition is immunosuppressant with an  $IC_{50}$  of 100 nM or less;

- c. conducting therapeutic profiling of the composition for efficacy and toxicity in animals;
  - d. preparing a package insert describing the use of the composition for immunosuppression therapy; and,
  - e. marketing the composition for use as an immunosuppressant.
113. **(Withdrawn)** A method for conducting a life science business comprising:
- a. isolating one or more antigen-binding domains that bind to MHC class II expressed on the surface of human cells with a  $K_d$  of 1  $\mu$ M or less;
  - b. generating a composition comprising said antigen-binding domains, which composition is immunosuppressant with an  $IC_{50}$  of 100 nM or less;
  - c. licensing, jointly developing or selling, to a third party, the rights for selling the composition.
114. **(Withdrawn)** The method of any of claims 112 or 113, wherein the antigen-binding domain is isolated by a method which includes:
- a. isolation of VL and VH domains of human composition from a recombinant antibody library by ability to bind to HLA-DR,
  - b. generating a library of variants at least one of the CDR1, CDR2 and CDR3 sequences of one or both of the VL and VH domains, and,
  - c. isolation of VL and VH domains from the library of variants by ability to bind to HLA-DR with a  $K_d$  of 1  $\mu$ M or less.
115. **(Withdrawn)** The method of any of claims 109, 110, 112, and 113, wherein said antigen-binding domain comprises a combination of VH and VL domains found in the clones selected from the group consisting of MS-GPC-1, MS-GPC-8, MS-GPC-10, MS-GPC-8-1, MS-GPC-8-6, MS-GPC-8-9, MS-GPC-8-10, MS-GPC-8-17, MS-GPC-8-18, MS-GPC-8-27, MS-GPC-8-6-2, MS-GPC-8-6-19, MS-GPC-8-6-27, MS-GPC-8-6-45, MS-

GPC-8-6-13, MS-GPC-8-6-47, MS-GPC-8-10-57, MS-GPC-8-27-7, MS-GPC-8-27-10 and MS-GPC-8-27-41.

116. **(Withdrawn)** A host cell harboring a vector of claim 40.
117. **(New)** The composition of claim 24, wherein said antigen-binding domain further comprises a VL CDR1 sequence represented in the general formula  
SGSXXNIGXNYVX (SEQ ID No. 6)  
wherein each X independently represents any amino acid residue.
118. **(New)** The composition of claim 117, wherein the VL CDR1 sequence is  
SGSESNIGNNYVQ (SEQ ID No. 7).
119. **(New)** The composition of any of claims 22-29, wherein said antigen-binding domain binds to human HLA-DR.
120. **(New)** The composition of claim 119, wherein said antigen-binding domain binds to human HLA-DR with a  $K_d$  of 1  $\mu$ M or less.
121. **(New)** The composition of claim 119, wherein said antigen-binding domain binds to the  $\alpha$ -chain of HLA-DR.
122. **(New)** The composition of any of claims 22-29, wherein said multivalent polypeptide has an  $EC_{50}$  of 100 nM or less for killing activated lymphoid cells.
123. **(New)** The composition of claim 67 or 70, wherein said antigen-binding domain binds to the  $\alpha$ -chain of HLA-DR.
124. **(New)** The composition of claim 82, wherein said antigen-binding domain further comprises a VL CDR1 sequence represented in the general formula  
SGSXXNIGXNYVX (SEQ ID No. 6)  
wherein each X independently represents any amino acid residue.

125. (New) The composition of claim 124, wherein the VL CDR1 sequence is SGSESNIGNNYVQ (SEQ ID No. 7).
126. (New) A human IgG antibody generated by cloning into an immunoglobulin expression system an antigen-binding domain of human composition with binding specificity for human HLA-DR antigen, wherein;
- (a) treating cells expressing said antigen with said IgG causes or leads to killing of said cells in a manner where neither cytotoxic entities nor immunological mechanisms are needed for said killing; and
- (b) said antigen-binding domain includes a combination of a VH and a VL domain, wherein said combination is found in one of the clones selected from the group consisting of: MS-GPC-8-6-13 (SEQ ID NOS 41 and 54, respectively), MS-GPC-8-10-57 (SEQ ID NOS 41 and 56, respectively) and MS-GPC-8-27-41 (SEQ ID NOS 41 and 58, respectively).
127. (New) The human IgG antibody of claim 126, wherein the IgG antibody is an IgG<sub>4</sub> antibody.
128. (New) A human IgG antibody generated by cloning into an immunoglobulin expression system an antigen-binding domain of human composition with a binding specificity for human HLA-DR antigen, wherein;
- (a) treating cells expressing HLA-DR with said IgG causes or leads to suppression of an immune response; and
- (b) said antigen-binding domain includes a combination of a VH and a VL domain, wherein said combination is found in one of the clones selected from the group consisting of: MS-GPC-8-6-13 (SEQ ID NOS 41 and 54, respectively), MS-GPC-8-10-57 (SEQ ID NOS 41 and 56, respectively) and MS-GPC-8-27-41 (SEQ ID NOS 41 and 58, respectively).
129. (New) The human IgG antibody of claim 128, wherein the IgG antibody is an IgG<sub>4</sub> antibody.